

## Platelet Dysfunction Associated With Insulin Therapy in Patients With Type 2 Diabetes: Please Do Not Throw the Baby Out With the Bathwater!

André J. Scheen, MD, PhD Delphine Legrand, MD

*Division of Diabetes, Nutrition, and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, University of Liège, Liège 4000, Belgium*

We read with interest the study by Angiolillo et al. (1) demonstrating that patients with type 2 diabetes have increased platelet aggregation on dual aspirin-clopidogrel therapy and that patients with insulin-treated diabetes mellitus (ITDM) have greater adenosine diphosphate (ADP)-induced platelet aggregation compared with patients with non-insulin-treated diabetes mellitus (NITDM) (1). This is an important observation as 42% of 15,603 randomized patients (in the CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance] trial) had diabetes (17% treated with insulin), with no significant better cardiovascular protection of the clopidogrel plus aspirin combination versus aspirin alone (2). However, Angiolillo et al.'s (1) finding and interpretation might be considered by cardiologists as a counterproductive effect of insulin therapy and represent an erroneous argument for not switching to insulin those numerous type 2 diabetic patients with poor glucose control while on oral treatment.

Type 2 diabetes is a progressive disease. Even if it is true that patients with ITDM are at a more advanced stage of their metabolic disorder, the need to switch to insulin reflects profound insulin secretory defect rather than more severe insulin resistance (3,4), as erroneously stated by Angiolillo et al. (1). That the higher proportion of women among ITDM subjects may be considered as an argument supporting the insulin-resistance hypothesis should also be challenged, as greater insulin resistance in women than in men is not a classical finding if appropriately measured (5).

Besides glucose-lowering therapy, the most important clinically relevant difference between the 2 groups was the 1% difference in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level (7.9% in ITDM patients vs. 6.9% in those with NITDM,  $p < 0.001$ ), that is, the same difference as that reported in the intensive group versus the conventional group in the United Kingdom Prospective Diabetes Study (6). Angiolillo et al. (1) suggested that this 1% difference could not explain the difference in platelet reactivity as HbA<sub>1c</sub> levels were not correlated with any of the platelet-function assays performed. This finding is in contrast to other observations showing a significant influence of glucose levels on platelet reactivity and effect of antiplatelet agents (7). According to Angiolillo et al. (1), the study was conducted in a tightly controlled diabetic population, which led to a limited variability in HbA<sub>1c</sub> levels; however, the reported 6% coefficient of variation of HbA<sub>1c</sub> levels looks astonishingly low with regard to the mean  $\pm$  SD data of the 2 subgroups ( $7.9 \pm 1.5\%$  vs.  $6.9 \pm 1.0\%$ ).

A key message from the study by Angiolillo et al. (1) is that aggressive and/or tailored antithrombotic regimens for high-risk patients such as diabetic patients may be warranted. However, emphasizing in the "therapeutic implications" section that "treatment with insulin is typically considered a surrogate of increased atherothrombotic risk" may be misleading. Although this remains a controversial issue, numerous data do not support this statement (8). As diabetologists, the key objective is to obtain adequate metabolic control (HbA<sub>1c</sub>  $<7\%$  and ideally  $<6.0\%$ ), in combination with aggressive management of all other cardiovascular risk factors, including effective antiplatelet therapy (9). In numerous patients, insulin therapy is a necessary and often irreplaceable partner to tackle hyperglycemia and reach HbA<sub>1c</sub> targets. Please do not throw the baby out with the bathwater!

### REFERENCES

1. Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol* 2006; 48:298-304.
2. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
3. Scheen AJ, Lefèbvre PJ. Insulin resistance vs. insulin deficiency: which comes first? The old question revisited. In: Di Mario U, Leonetti F, Pugliese G, Sbraccia P, Signore A, editors. *Diabetes in the New Millennium*. New York, NY: Wiley, 2000:101-13.
4. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003;46:3-19.
5. Ferrannini E, Natali A, Bell P, et al. Insulin resistance and insulin secretion in obesity. *J Clin Invest* 1997;100:1166-73.
6. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

7. Watala C, Boncler M, Gresner P. Blood platelet abnormalities and pharmacological modulation of platelet reactivity in patients with diabetes mellitus. *Pharmacol Rep* 2005;57 Suppl:42-58.
8. Muis MJ, Bots ML, Grobbee DE, Stolk RP. Insulin treatment and cardiovascular disease: friend or foe? A point of view. *Diabet Med* 2005;22:118-26.
9. American Diabetes Association. Standards of medical care in diabetes mellitus—2006. *Diabetes Care* 2006;29 Suppl 1:S4-S42.

## **Reply**

We appreciate the comments raised by Drs. Scheen and Legrand. In their letter, they reveal a status of "apprehension" toward the potential impact of our study (1) on how clinicians may approach glucose-control management, in particular, avoiding switching to insulin in patients not well controlled on oral glucose-lowering medication. Recognizing the importance of the concerns raised regarding the potential unintended effects of our investigation (1) this was neither the intent nor the correct interpretation of our findings.